UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	4

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
09/600,493	WANDS ET AL
Examiner	**Art Unit**
Christopher Drabik	1633

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

Detailed Action

Informalities

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 18 – 34 have been renumbered to reflect the omission of a claim 17.

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification contains spelling and grammatical errors terms which make the text unclear . The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose usage in the specification are: page 9 at line 16, page 9 at line 30 and page 17 at line 13.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 USC 119 a-d or e as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37CFR 1.78).

Applicant, in response to this office should amend the first page of the specification to contain priority data.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9-16 rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for generating a prophylactic or therapeutic immunity in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 9 –16 are drawn a pharmaceutical composition comprising a recombinant nucleic acid comprising the non-structural proteins of HCV. As a pharmaceutical composition, the claims imply an in vivo use of the nucleic acid to provide a prohylactic or therapeutic response. In a narrow interpretation of the claim they are directed simply

to a product that can be administered to an animal. It is acknowledged that one of skill in the art could ***make*** the claimed invention, however, the specification does not enable ***use*** of the invention. The applicant teaches that the claimed pharmaceutical composition can elicit a form of humoral and cellular immune response when administered to mice. However, this data cannot be extrapolated to humans because mice are not a good model system for HCV infection, primarily because mice cannot be infected with HCV. Simply showing that the an immune response can be elicited in mice, does not mean that the said nucleic acid would be sufficient to provide humans with a prophylactic or therapeutic immunity.

When reading claims 9-16 in light of the specification, the administration of the product encompasses a desired effect which is not intended to be mice. The specification clearly discusses the use of the recombinant HCV nucleic acid as a means for immunizing against or treating HCV infection in humans. See paragraph bridging page 7 and 8. While claims 9 - 14 do not recite a particular therapeutic use or effect, the breadth of in vivo use as disclosed in the claims anticipates a therapeutic usage in humans. In addition, when analyzing the enabled scope of the claims, the teachings of the specifications are to be taken into account because the claims are to be given their broadest reasonable interpretation that is ***consistent*** with the specification. The broadest reasonable interpretation of the claimed invention encompasses humans and is not enabled by the specification for the reasons that inducing a limited immune response in mice is not sufficient to predict a prophylactic immunity in humans.

The field of DNA vaccination in the area of HCV, while rapidly developing remains unpredictable. Thus Chattergoon et al. calls genetic immunization an 'emerging technology' (see Chattergoon et al. page 762, column 1, ¶3). The art is unpredictable. "[T]there is little evidence that the immune responses induced by these vaccines will be completely protective against any human pathogen" (see Chattergoon et al. page 762, ¶ bridging columns 1 and 2), and "...clinical applications of this form of technology remain elusive" (see McDonnell et al., page 42, ¶1). Chattergoon et al. explains that though the success in animal models has sparked interest and raised hopes, there is no evidence in humans (see page 762, ¶ bridging columns 1-2).

As recently as November 1999, Houghton writes that although the field holds great promise, "Future challenges in this area include reproducing in primates the broad immune responses so far observed in mice and proving efficacy in the chimpanzee model." (Houghton, 1999 To extrapolate from this statement, without evidence that an HCV nucleic acid vaccine is effective in primates, it is premature to expect that a vaccine tested in mice would be effective in humans. It should be noted that the chimpanzee model had been used in testing the efficiency of anti HCV vaccination at least one year prior to the filing of the instant application. (Farci et al 1996) Applicant discloses no evidence for attempting to prove efficacy of claimed recombinant nucleic acids in this model system. Houghton continues; "The delivery of the HCV nucleic acid needs to be optimized since most mouse protocols involve the injection of several hundred micrograms of DNA in order to get generally weak immune responses." This statement implies that added experimentation beyond mouse vaccination is required to

translate the results of mice experiments to primates. Despite the fact that the efficacy of the claimed nucleic acid vaccine has not even been established in primates, the applicants claim the method as being effective in humans.

Given the state of the art, the lack of predictability thereof, the amount of guidance provided, the lack of applicable working examples, and the amount of experimentation necessary to practice the invention, it is concluded that one of skill in the art would require an undue amount of experimentation in order to practice the invention. Since the disclosure of the specification does not support the recitation of claims 9-16 rejection under 35 USC 112 (1) is appropriate.

Claim 17-33 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 17-33 include a method of using the recombinant nucleic acid recited in claim 1 as a means for eliciting an immune response in humans. For reasons cited above, interpretation of the term "immune response" must be made through a reading of the specifications. The specification states explicitly that administration of the recombinant nucleic acid described in the application is intended to "prophylactically and/or therapeutically immunize or treat an individual against HCV".

Claim 17 is drawn to a method of administering the nucleic acid of Claim 1 in an amount ***effective*** to induce an immune response in humans against hepatitis C. While any amount of DNA administered to a human might induce an immune response, the claims read in light of the specification indicate an effective amount which confers a

preventive immunity. The specification clearly discloses amounts of nucleic acid to be administered to mice in which a limited immune response can be elicited, however this data cannot be extrapolated to humans for reasons set forth above. Since mice cannot be infected with HCV, the mouse model is inadequate to judge whether protective immunity against HCV can be generated by any sort of inoculation. Claims 18-33, while modifying the scope of claim 17, nonetheless are deficient in that they depend essentially upon the ability to induce an effective immune response in humans. The basis for rejection of claims 17-33 is, therefore, made on the same grounds of rejection as that for claims 9-16.

Claim 29,30 and 31 Claims 29 and 30 pertain to the immunization of a human susceptible to hepatitis C through administration of a pharmaceutical composition comprising a nucleic acid comprising HCV non-structural proteins. Claim 31 is a method for administering the nucleic acid alone. Although the claims are dissimilar in that no carrier or diluent is specified in claim 31, the treatments outlined in claim have the same stated effect: A preventive treatment for HCV infection in humans. These claims in essence are redundant to claims 17 and 23 and it is, therefore, appropriate to reject claims 29-31 over the same grounds as claims 17-23. Specifically the reasons for rejecting 29 – 31 are: 1.) not furnishing adequate guidance in using the invention, 2.) not disclosing a sufficient model system to enable the invention, 3.) undue experimentation is required to perform the invention as claimed.

Claim 32 and 33 involve a therapeutic treatment for a human infected with HCV. The term therapeutic treatment encompasses effecting the course of a viral

infection in such a way that the adverse nature of the infection are diminished or alleviated. There is no basis in the claims or specifications for reasonably believing that the methods described in claims 32 and 33 will function in this manner. The applicant has shown that mice inoculated with an HCV nucleic acid vaccine produces humoral and cellular responses specific to the non-structural proteins of HCV, however, no evidence is given that the response is sufficient to decrease the effects of a viral infection. So, no interpretation of the therapeutic benefits of the vaccine can be drawn in mice and certainly none can be assumed for humans.

Given the state of the art, the lack of predictability thereof, the amount of guidance provided, the lack of applicable working examples, and the amount of experimentation necessary to practice the invention, it is concluded that one of skill in the art would require an undue amount of experimentation in order to practice the invention. Since the disclosure of the specification does not support the recitation of claims 17-33 rejection under 35 USC 112 (1) is appropriate.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

Claim 1, 2, 4 and 8 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Selby et al. (1993) The basis for the claims 1, 2, and 4 is a recombinant nucleic acid molecule comprising sequences from the non-structural proteins of HCV. Claim 8 is a

cell line transduced with the recombinant nucleic acid of claim 1. Numerous examples in the prior art teach the use of recombinant vectors for experimentation involving the non-structural proteins of HCV. In particular Selby et al teaches recombinant nucleic acid vector constructs encompassing the non-structural proteins of HCV. (see specifically p1104). This reference clearly anticipates Claim 1 of the instant application. The recombinant vectors described in therein include nucleic acid sequences encoding non-structural proteins 3, 4 and 5. At least 50 amino acids of each protein are encoded for in the vectors taught by Selby et al. Hence, claims 2 and 4 are also clearly anticipated. The experimentation of Selby et al includes the generation of recombinant cells comprising nucleic acids comprising the non-structural proteins. Since literature cited above indicates the use of recombinant nucleic acids comprising the non-structural proteins and cells thereto as delineated in Claims 1, 2 ,4, and 8 it is appropriate to reject these under 35 USC 102 (b).

Claim 1-4 rejected under 35 U.S.C. 102(b) as being clearly anticipated by D'Souza et al(1995). Claim 3 discloses a fusion protein comprising the HCV non-structural proteins 3.4 and 5. Teaching in the literature includes vectors consisting of HCV non-structural proteins linked to amino acid motifs commonly used to simplify the purification of proteins. In particular, this fusion protein technique has been used in the purification of amino acids comprising HCV NS3 (D'Souza see page 1730) This reference clearly anticipates the language "fusion protein encoding NS3. NS4. or NS5 or any combination thereof" as cited in claim 3. D'Souzas' disclosed recombinant

nucleic acids comprise an HCV nonstructural protein. The coding sequence of the nucleic acid contains at least 50 amino acids of the protein. Since D'Souza clearly anticipates claims 1-4 rejection of claims 1-4 under 35 USC 102 (b) is appropriate.

Claims 1, 2, 4, 5 and 8 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Harada et al. Claim 5 encompasses a nucleic acid comprising HCV non-structural protein coding sequences operably linked to regulatory elements functional in human cells. Harada et al teaches the generation of a human hepatoma cell line which constituitively expresses the non-structural proteins of HCV. In order to ensure protein expression, the vector used for transformation of the cells included the human EF 321 promoter. (See Harada et al p 1216 col 1 para 1) Since proteins were indeed expressed in this cell line the promoter was operabley linked to the coding sequence. Hence, the recombinant nucleic acid construct clearly anticipates the language of claim 5 of the instant application.

Claim 8 encompasses recombinant cells comprising nucleic acids comprising the non-structural proteins. Numerous examples in the literature disclose recombinant host cell lines transformed transiently or stabley with nucleic acids comprising the HCV non-structural proteins. One example is the work of Harada et al cited in the previous paragraph. In the disclosure of Harada et al, vectors containing the coding sequence for HCV non-structural proteins were used to stabley transform human HepG2 cells (see paragraph bridging pages 1216 and 1217, page 1217 subsequent three paragraphs).

Claims 1, 2 and 4 are anticipated by Harada et al because the recombinant nucleic acids described therein meet the scope of the nucleic acids delineated in claims 1, 2, and 4. Specifically, the recombinant nucleic acid constructs of Harada comprise HCV non-structural proteins. This clearly anticipates Claim 1 of the instant application. The recombinant vectors described therein include nucleic acid sequences encoding HCV non-structural proteins 3, 4 and 5. At least 50 amino acids of non structural protein is encoded for in the vectors taught by Harada et al. Hence, claims 2 and 4 are also clearly anticipated

As explained in the preceding three paragraphs, claims 1, 2, 4, 5 and 8 falls within the scope of the recombinant nucleic acids and cells described by Harada et al and, therefore, rejection under 35 USC 102(b) is appropriate.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-13 rejected under 35 U.S.C. 103(a) as being unpatentable over Selby et al in view of Selden et al.

Claims 9-13 of the instant application describe recombinant nucleic acids comprising the non-structural proteins of HCV as part of a pharmaceutical composition. In describing the pharmaceutical composition, applicant writes at page 13 line 19:"The genetic vaccines according to the invention are formulated according to the mode of administration to be used." Earlier in the specification it is stated that one of the routes of administration may be oral. (Page 12 line 9) This implies that **any** diluent which might be taken orally is suitable as part of the claimed pharmaceutical composition. Applicant specifies certain formulations of the pharmaceutical composition which are acceptable: "In some cases an isotonic formulation is used. In some cases, isotonic solutions such as phopsphate buffered saline is used" (pg 13 lines 29 and 31)

Selby et al teaches recombinant nucleic acids comprising the non-structural proteins of HCV. Specifically he describes the construction of vectors which include the nonstructural proteins of HCV. Although, it is commonly accepted practice in the art to

resuspend nucleic acids in isotonic solutions. Selby et al does not specify the solution into which said nucleic acid is diluted.

Selden et al (1987) teaches the preparation of recombinant nucleic acids (see page 9.2.1) . The preparation of nucleic acids included the solubilization of purified nucleic acids in tris buffered saline. Tris buffered saline can be an isotonic solution and can be considered pharmaceutical a carrier based on the instant specification.

One of ordinary skill in the art would have been motivated to resuspend a nucleic acid comprising HCV nonstructural proteins in a pharmaceutically accepted buffer because nucleic acids can be easily dissolved in isotonic solution, solutions such as TBS or water, and this is routine in the art. Therefore the invention as a whole would have been prima facie obvious to one of skill in the art at the time the invention was made.

Claims 7, 8 and 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Selby et al. Selby et al teaches recombinant nucleic acids comprising the non-structural proteins of HCV. Specifically he describes the construction of expression vectors comprising the non-structural proteins of HCV. Selby et al provides evidence that the non-structural proteins are expressed in human cells. However, said expression vectors are designed such that transcription requires the presence of T7 polymerase. Hence co-infection with a vaccinia virus vector containing the T7 polymerase is required. Selby et al does not teach that eukaryotic regulatory elements can be used in an expression vector system to drive production of the HCV non-structural proteins.

The CMV promoter, Rous sarcoma virus enhancer and various polyadenylation signals are nucleic acid elements that are well known in the art and are commonly used in eukaryotic cells for the expression of proteins. It is routine in the art to substitute promoters and enhancers to modulate expression levels. It is further noted that expression vectors containing various enhancers, promoters and polyadenylation signals were commercially available at the time of filing the instant application . In fact, the vector used to generate the recombinant nucleic acid of claim 7 was purchased from a commercial vendor, Apollon.

One of ordinary skill in the art would have been motivated to combine the HCV recombinant nucleic acid sequence described by Selby et al with the CMV promoter and Rous sarcoma virus enhancer containing vector from said commercial source to modulate expression. One of skill in the art has the ability to make such eukaryotic expression vectors comprising combinations of enhancers, promoters and polyadenylation and would readily expect success Therefore the invention as a whole would have been prima facie obvious to one of skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 703-305- 4051. The fax phone

number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-308-4242.

Deborah Clark

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600